Baseline Correction in Bioequivalence Studies for Drug Products Containing An Endogenous Compound

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BACKGROUND:

- For bioequivalence (BE) assessment, baseline correction is generally considered for a drug product containing an endogenous compound.
- The FDA recommends either a time-averaged or time-matched method for baseline correction.[1]
- This project aimed to identify current recommendations in product-specific guidances (PSGs) to determine a consistent approach for baseline correction method recommendations.

METHODS:

- A survey of PSGs for drug products containing endogenous compounds was conducted.
- Testosterone (T) having circadian rhythm was investigated and T measurements obtained in bioavailability (BA) and BE studies submitted in the approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs), respectively were analyzed.
- To assess endogenous T variation within a day,
  - fluctuation within a study period was computed from individual subject as [(highest value – lowest value)/C_{max}] and
  - intrasubject variability (CV%) across all time points within a study period was calculated.
  - 90% confidence interval (CI) of two different methods were obtained.

RESULTS:

- Thirty-nine active pharmaceutical ingredients (APIs) consisting of 68 PSGs for drug products containing endogenous compounds were identified.
- The correction method for the same API was consistent across different dosage forms.
- % fluctuation was around 20% in the BA study and 10% in the BE study.
- %CV across all time points within a study period was low in T.
- 90% CI was comparable when results derived from time-averaged and time-matched methods were compared.

Reference: 1. U.S. Food and Drug Administration. (2021). *Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an abbreviated new drug application*.

Majority (53/68) of **product-specific guidances** for drug products containing **endogenous compounds** recommend the **time-averaged** baseline correction method.

Our analysis suggested that when measuring **testosterone** level in **hypogonadal males**, **time-averaged** baseline correction method may be considered.

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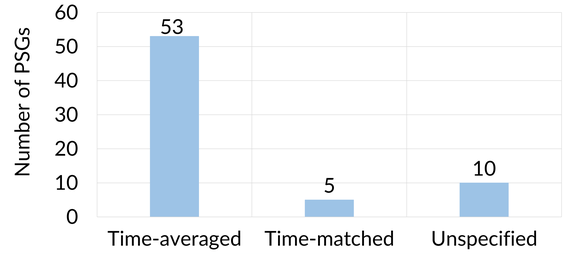
Distribution among baseline correction methods of 68 PSGs for drug products containing endogenous compounds

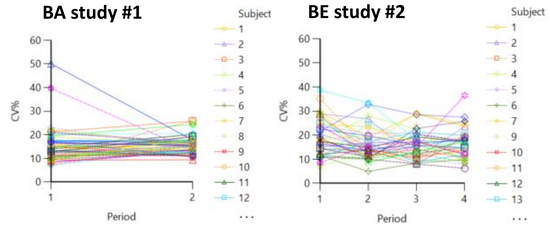


Endogenous T variation within a day

Fluctuation calculation

	BA study #1 (n=20)	BE study #2 (n=42)
% Fluctuation (mean ± SD)	20.49% ± 8.26%	9.79% ± 7.38%

CV% across all time points within a study period



Statistical summary of baseline-corrected unscaled data from BE study #2

	Time-averaged		Time-matched	
Fasted	Lower CI	Upper CI	Lower CI	Upper CI
AUCt	92.26	104.65	93.42	105.35
AUCi	95.98	111.56	101.14	116.93
Cmax	88.79	103.15	90.38	103.93

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Disclaimer: The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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